

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**  
**(Case No. 05-159-A)**

In the Application of:	)	
	)	
Robert Danziger	)	Examiner: Baek, Bong-Sook
	)	
Serial No. 10/588,673	)	
	)	
Filing Date: September 17, 2007	)	Group Art Unit: 1614
	)	
Int'l. Filing Date: 22 February 2005	)	
	)	
For: Blood Pressure Reduction in	)	Confirmation No.: 9232
Salt-Sensitive Hypertension	)	

**DECLARATION OF DR. ROBERT DANZIGER UNDER 37 C.F.R. §1.132**

I, Robert Danziger, declare as follows:

1. I am a citizen of the United States, currently residing at 175 East Delaware Place, Apt. 8105, Chicago, Illinois.
2. I am an Associate Professor of Medicine, Physiology and Pharmacology at the University of Illinois at Chicago. I have published in peer-reviewed journals in the field of cardiac hypertrophy and hypertension. Attached as Exhibit A is my *curriculum vitae*.
3. I am the sole inventor of the above-referenced application, Serial Number 10/588,673, filed on September 17, 2007 (the '673 application). Claim 1 of the '673 application reads "[a] method of treating salt-sensitive hypertension in a mammal suffering therefrom, said method comprising the step of administering a therapeutically effective amount of a cyclic nucleotide phosphodiesterase (PDE) inhibitor to said mammal."
4. I understand that the Patent Office has rejected the claims currently pending in the '673 application based on the disclosure of Barone *et al.* (WO2004/105751).

5. Specifically, I understand that the Patent Office takes the position that the Barone reference teaches the use of a PDE inhibitor, such as rolipram, to treat hypertension.
6. On the contrary, the Barone reference has not demonstrated any effects of any PDE inhibitors on hypertension, let alone salt-sensitive hypertension. Barone *et al.* disclosed results purportedly demonstrating that a PDE inhibitor, rolipram, reduced cardiac hypertrophy in mice. The Barone reference further speculated that the inhibitor might also be used to treat other cardiovascular pathologies in a mammal. This mere speculation is insufficient to inform a person experienced in the field that a PDE inhibitor can be used to treat *hypertension*.
7. Cardiac hypertrophy is a disease of many etiologies. Although hypertension may cause pressure overload, which may in turn lead to cardiac hypertrophy, cardiac hypertrophy can arise from etiologies completely unrelated to blood pressure buildup. For example, hypertrophic cardiomyopathy is an inherited cardiac muscle disorder manifested by the thickening of heart muscle that is not caused by hypertension; in another example, amyloidosis in the heart can lead to cardiac hypertrophy but has no relation to hypertension.
8. Therefore, a drug that reduces hypertension may help alleviate hypertrophy; however, the reverse is not always true, *i.e.*, a drug that reduces hypertrophy does not always reduce blood pressure and thus does not necessarily reduce hypertension.
9. Even in hypertension-induced hypertrophy, a drug that alleviates hypertrophy does not necessarily reduce the underlying cause of hypertension. For example, Ito *et al.* showed in 1993 that the endothelin receptor antagonist BQ123 reduced cardiac hypertrophy provoked by left ventricular overload in rats. The drug, however, exhibited no effects on aortic pressure in the animals. See Ito *et al.* 1993, *Circulation* 89:2198-2203, particularly p. 2199, 2<sup>nd</sup> col. and Table 1. Similarly, Date *et al.* demonstrated that the antioxidant N-2-Mercaptopropionyl glycine (MPG) attenuated pressure overload-induced cardiac hypertrophy in mice; however, MPG was ineffective in reducing high blood pressure -- the underlying cause of hypertrophy in the animals. See Date *et al.* 2002 *J. American*

*College of Cardiology* 39:907-912, particularly p. 909, 1<sup>st</sup> col. and Table 1. The Ito reference and the Date reference are attached to this Declaration as Exhibits B and C, respectively.

10. Further, it was known as of 2003 that effective therapy for hypertrophy does not always reduce blood pressure in an animal that experiences hypertrophy and also suffers from hypertension. See Nakagami et al. 2003, *J. Molecular Cellular Cardiology* 35:851-59 (Exhibit D).
11. The Nakagami reference used a mouse model that exhibits angiotensin II-induced hypertrophy and angiotensin II-induced hypertension. The reference showed that the antioxidant, N-acetylcysteine (NAC), was effective in attenuating angiotensin II-induced cardiac hypertrophy. See Abstract. However, angiotensin II-induced increase in blood pressure was not affected by the treatment of NAC. See page 856, section 3.6 of the Nakagami reference.
12. Therefore, a person experienced in the field of cardiovascular pathology would have known that a drug that reduces cardiac hypertrophy is not always effective in treating hypertension, much less salt-sensitive hypertension. Additionally, a person experienced in the field would have known that a drug that reduces cardiac hypertrophy does not necessarily reduce hypertension in a mammal that suffers from both hypertrophy and hypertension.
13. Thus, I conclude that Barone's mere speculation that a PDE inhibitor might be used to treat cardiovascular pathologies is insufficient to inform a person experienced in the field that a PDE inhibitor can be used to treat salt-sensitive hypertension.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States

Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Respectfully submitted,

Dated: March 10, 2010

By: Robert Danziger

Robert Danziger, M.D.